

REMARKS

This document is submitted in reply to the Office Action dated November 16, 2007 (Office Action).

Applicants have cancelled claims 51 and 53 and withdrawn claims 23-26, 29, and 36. Claims 27, 30, 38, 42, 47-50, 52 and 54 have been amended to more particularly point out what they regard as their invention.

Upon entry of these amendments claims 27-28, 30-35, 37-38, 39-50, 52, and 54 will be under examination. Applicants respectfully request that the Examiner reconsider this application in view of the following remarks.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 27-28, 31-43 for failing to comply with the written description requirement. More specifically, he rejects claims 27 and 38 for reciting the phrases “organic acid ester” and “ester of an aliphatic or aromatic acid,” respectfully, on the ground that they “are not defined in the specification so as to ascertain structures of the compounds included and/or excluded by the phrases [as the] only esters disclosed [] are compounds of formula IV of claim 29.” See the Office Action page 2, lines 14-18.

Applicants have amended claims 27 and 38 to include formula IV. As amended, claims 27 and 38 define the compounds that are encompassed by the phrases “organic acid ester” and “ester of an aliphatic or aromatic acid.” Accordingly, claims 27-28, and 31-43 now comply with the written description requirement. Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 26-46, 51-54 are rejected for being indefinite. Applicants have cancelled claims 51 and 53 and withdrawn claims 26, 29, and 36.

As discussed above, claim 27-28, and 31-43 have been amended to define the compounds that are encompassed by the phrases “organic acid ester” and “ester of an aliphatic or aromatic acid.” Thus, these claims, as amended, are definite.

Concerning claim 30, Applicants submit that all compounds recited in this claim are esters of organic acids of the general formula set forth in claim 27, from which claim 30 depends:



Applicants have amended claim 27 to specifically define R_6 and R_7 . To address the Examiner's concerns (see the Office Action, page 3, lines 7-10), Applicants submit that, with the added definitions of R_6 and R_7 in claim 27, one of ordinary skill would understand that $R_6\text{-COO}$ represents benzoate (benzyl-COO), heptanoate (C_6 alkyl-COO), octanoate (C_7 alkyl-COO), laurate (C_{11} alkyl-COO), myristate (C_{13} alkyl-COO) or palmitate (C_{15} alkyl-COO), and R_7 is methyl, ethyl, propyl or butyl. Thus, claim 30 is also definite.

Turning to the rejection of claims 38 and 44-46 for their reference to figures, Applicants have amended claim 38 to remove the reference to Figure 2 and traverse below the Examiner's ground for rejecting claims 44-46.

According to MPEP 2173.05(s):

... Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

Claims 44-46 cover specific crystals characterized by their X-ray diffraction analysis shown in Figures 2, 4, and 6 of the Specification. See pages, 17, 20, and 23. Applicants submit that this is an exceptional circumstance. There is no practical way to define these structures in words and it is more concise to incorporate by reference than duplicating the Figures 2, 4, and 6 into the claims. The incorporation by reference of

these figures was made out of necessity, not out of convenience. Thus, claims 44-46 are definite.

The Examiner further rejects claims 44-45 on the ground that they are duplicates of claim 1. Claim 1 was previously cancelled. The Examiner concurred with this cancellation. See the Office Action, page 2, line 2. Indeed, claims 44-45 are not duplicates. As this rejection is improper, Applicants respectfully request its withdrawal.

Claim 52 covers a fluorescein-containing pharmaceutical composition and Claim 54 covers a fluorescein-containing labeling composition. As a pharmaceutical composition requires different ingredients than a labeling composition, Applicants submit that claims 52 and 54 are not duplicates of each other.

Rejection under 35 U.S.C. § 102

The Examiner rejects certain claims for anticipation, citing as many as four references. Applicants respectfully traverse below.

I

The Examiner rejects claims 45-46 and 49-50 as anticipated by Monsanto, German Patent No. DE360691 (Monsanto).

Claims 45 and 49 cover crystals of 4', 5'-dimethylfluorescein, whereas claims 46 and 50 cover crystals of 4', 5'-dihydroxyfluorescein.

As correctly pointed out by the Examiner, Monsanto teaches "gallein made by condensing phthalic anhydride with pyrogallol." See the Office Action page 4, line 14.

Gallein is a fluorescein containing a xanthene ring, in which a hydroxyl group occupies the 4' and 5' position of the ring. Monsanto does not teach a compound in which the 4' and 5' positions are occupied by methyl groups, as required by the compounds recited in claims 45 and 49. Accordingly, Monsanto does not anticipate claims 45 and 49.

The Examiner goes on to state that, "[t]hough [] the claims are limited and defined by their process of making, the products are unpatentable if they are the same [as] or obvious from the product of a prior art." See the Office Action, page 4 lines 18-20.

As described in the Specification, the crystals of claims 46 and 50 were obtained by acidification of the crude product, in an organic medium (e.g., ethanol/acetone mixture). This purification method, covered by claim 35, proceeds via a solubilization phase. During solubilization, the impurities are released into the solvent and eliminated from the crystals. See the Specification page 11, lines 1-2 and 12-19. As described in the International Preliminary Examination Report, copy attached hereto as "Exhibit A," the Monsanto method uses no solvent. See page 4, last paragraph. In other words, Monsanto does not teach a purification that proceeds through a solubilization phase. For this reason, Applicants submit that the products obtained by the Monsanto method differ from the crystals covered by claims 46 and 50. Accordingly, Monsanto does not anticipate claims 46 and 50.

II

The Examiner also rejects claims 23-26, 44, 47-48, and 51-54 as being anticipated by Sujeeth, US Patent No. 5,637,733 (Sujeeth), Burdette et al., J.Am.Chem.Soc., Vol 123, pp. 7831-7841 (Burdette), or Singh, US Patent No. 6,514,700 (Singh). Claim 51 and 53 have been cancelled and claims 23-26 have been withdrawn.

Claim 44 covers a yellow-colored fluorescein crystal having the specific X-ray diffraction analysis (shown in Figure 2 of the Specification).

It is the Examiner's position that Sujeeth, Burdette, or Singh anticipates this specific structure. Applicants disagree.

None of Sujeeth, Burdette, and Singh cited teach a crystal structure of a yellow-colored fluorescein, let alone one having the diffraction analysis of Fig. 2. Thus, Applicants submit that these three references do not anticipate claim 44.

Both claims 47 and 48 cover phthalein crystals of formula I. The crystals covered by these two claims are obtained via the above-discussed purification process involving acidification of the crude product. None of Sujeeth, Burdette, and Singh teaches this acidification process. This process leads to two unique consequences: (1) extremely high purity to the produced crystals of phthaleins, and (2) a particular structure of the phthaleins crystals. Applicants submit a test report (Test Report) together with a

declaration (Declaration) signed by Francois Scherninski to support the conclusion of a particular structure, which are attached hereto as "Exhibit B" and "Exhibit C," respectively. The Test Report shows data comparing the physical properties of the crystals obtained by this purification method and crystals obtained according to known methods. Applicants would like to point out that, of the three cited references, only Sujeeth specifically discusses how compounds having greater purity can be obtained. See column 4, lines 7-11 (reproduced below).

"If materials of higher purity are required, this can be accomplished by conventional methods, e.g. dissolve in base, treat with activated carbon, filter and precipitate with acid, or dissolve the soluble impurities in solvents such as n-butanol, DMF etc."

Given this teaching, Applicants compared the crystal structure of phthaleins obtained by the above-described purification method (covered by claim 35) and phthalein crystals obtained by alkalizing and then acidifying in water as taught in Sujeeth. As indicated in the Declaration, the crystals obtained by the method claim 35 have a different crystal structure from that of the prior art, as well as different physical properties (in particular a different thermal behavior and different diffraction diagrams).

In view of the above-remarks, Applicants submit that the three references do not anticipate the phthaleins crystals covered by claim 47-48.

Claims 52 and 54 cover a pharmaceutical composition and labeling composition, respectively. The fluorescein in these compositions is obtained via the novel acidification method covered by claim 35. As discussed above, this method produces fluorescein crystals that have unique properties when compared with compounds taught by the prior art. Accordingly, Sujeeth, Burdette, and Singh also do not anticipate the compositions of claims 52 and 54.

Rejection under 35 U.S.C. § 103

Claims 44-54 are rejected for obviousness in view of Monsanto, Sujeeth, Singh, and Burdette, individually. Applicants have cancelled claims 51 and 53. The rejection against claims 44-50, 52, and 54 is respectfully traversed below.

Claims 44-50 cover crystals of various phthaleins. Claims 52 and 54 cover a pharmaceutical composition and a labeling composition containing fluorescein crystals, respectively.

Applicants have pointed out above that the crystals recited in these claims are neither disclosed nor suggested by Monsanto, Sujeeth, Singh, and Burdette. Furthermore, the purification method used to obtain these crystals is also not taught or suggested by the cited references. Applicants submit that the Examiner has not established a prima facie case of obviousness based on Monsanto, Sujeeth, Singh, and Burdette, individually.

Even if a prima facie case of obviousness had been established (which Applicants do not concede), it can be successfully rebutted by a showing of unexpected results.

As discussed above, the crystals recited in these claims were obtained by a specific purification method neither taught nor suggested by any of the references. This purification method confers the phthalein crystals obtained with a higher purity and a unique crystal structure when compared with crystals obtained by known methods. See the attached Test Report and Declaration. Applicants reiterate that this structure imparts different physical properties; in particular a different thermal behavior and different diffraction diagrams

For the reasons set forth above, claims 44-50, 52, and 54 are not rendered obvious by Monsanto, Sujeeth, Singh, and Burdette.

CONCLUSION

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of

Applicant(s) : Joanne Tran-Guyon et al.
Serial No. : 10/533,377
Filed : November 22, 2005
Page : 17 of 17

Attorney Docket No.: 65201-002US1

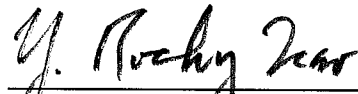
any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

The Petition for Extension of Time fee in the amount of \$60 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 50-4189, referencing Attorney Docket No. 65201-002US1.

Respectfully submitted,

Date: _____

3-17-08



Y. Rocky Tsao, Ph.D., J.D.
Attorney for Applicants
Reg. No. 34,053

Occhiuti Rohlicek & Tsao LLP
10 Fawcett Street
Cambridge, MA 02138
Telephone: (617) 500-2509
Facsimile: (617) 500-2499

Exhibit A

Translation

PATENT COOPERATION TREATY



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BCT030126	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/FR2003/003205	International filing date (day/month/year) 28 octobre 2003 (28.10.2003)	Priority date (day/month/year) 29 octobre 2002 (29.10.2002)
International Patent Classification (IPC) or national classification and IPC C07D 493/10		
Applicant LABORATOIRES SYNTH-INNOVE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet. <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u>10</u> sheets.
3. This report contains indications relating to the following items: I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 28 avril 2004 (28.04.2004)	Date of completion of this report 10 February 2005 (10.02.2005)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/FR2003/003205

I. Basis of the report

1. With regard to the **elements** of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
pages 1,2,4-7,9-24, as originally filed
pages _____, filed with the demand
pages 3,8, filed with the letter of 27 May 2004 (27.05.2004)
- ☒ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 1-22, filed with the letter of 27 May 2004 (27.05.2004)
- ☒ the drawings:
pages 1-6, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	3-14	YES
	Claims	1, 2, 15-22	NO
Inventive step (IS)	Claims	3-14	YES
	Claims	1, 2, 15-22	NO
Industrial applicability (IA)	Claims	1-22	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: US-A-5 637 733 (SUJEETH PUTHALATH K)
10 June 1997 (1997-06-10)

D2: DE 360 691 C (MONSANTO CHEMICAL WORKS)
6 October 1922 (1922-10-06)

D3: SHAWN C. BURDETTE ET AL.: "Fluorescent sensors for Zn²⁺ based on a fluorescein platform: Synthesis, properties and intracellular distribution" J. AM. CHEM. SOC, vol. 123, 2001, pages 7831-41, XP002248841

1. Corrections (PCT Article 28(2) and PCT Rule 91)

The corrections in claims 1 and 3 and the corresponding parts of the description are obvious (PCT Rule 91) and do not contravene PCT Article 28(2).

The correction in the new claim 12, which corresponds to the original claim 11, is acceptable since "crystal of red" clearly means "crystal of red colour".

Claims 8 to 11 are acceptable as concerns PCT Article 28(2).

2. Novelty (PCT Article 33(1))

The present application does not meet the requirements of PCT Article 33(1) as the subject matter of claims 1, 2 and 15 to 22 does not meet the novelty requirement of PCT Article 33(2).

D1 describes a method of producing fluorescein (examples 1 and 2) by condensing resorcinol with phthalic anhydride and without solvent. This teaching destroys the novelty of claims 1 and 2. The fact that the phthaleins in the present application are purer than the prior art compounds does not render the subject matter of the present application novel. Hence claims 15, 18, 19 and 22 are not novel either. D5 describes a method of purifying fluorescein. The resultant fluorescein can be used in pharmacy. This teaching proves that fluorescein can be purified and that a purified fluorescein is not novel. For a method to render a compound novel, all the prior art methods have to be incapable of purifying fluorescein (T 990/96). It appears possible to obtain a fluorescein by purification methods (e.g. D1). Therefore, the claims concerning purified fluorescein are not novel within the meaning of PCT Article 33(2).

In D1, example 3, 3,4,5,6-tetrachlorofluorescein is produced. The subject matter of example 3 destroys the novelty of claims 1, 2, 18 and 22.

D2 describes the production of phenolphthalein by condensation of phthalic anhydride with phenol and without solvent (example 1). In example 3, gallein (4',5'-dihydroxyfluorescein) is produced by the condensation of phthalic anhydride with pyrogallol, also without the use of a solvent. This teaching destroys the novelty of claims 1, 15, 17, 18, 21 and 22.

D3 describes the production of 4',5'-dimethylfluorescein (Experimental Section, production of compound 1). This subject matter destroys the novelty of claims 1, 16, 18, 20 and 22.

3. Clarity (PCT Article 6)

The application does not meet the requirements of PCT Article 6 since claims 15 to 17 are unclear.

The compounds in claims 15 to 17 are characterized by their colours and radio-crystallography spectra. These compounds are produced by the reaction of a red phthalein with an acid in an anhydrous solvent selected from the group comprising alcohols, ketones, ethers, halogenated solvents or mixtures thereof. In light of the description, it is not clear what happens to the phthaleins in the above-mentioned method. An acid addition salt of the phthalein compound may be formed after the reaction with an acid.

Exhibit B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In application of)
Tran-Guyon et al.)
Serial No. : 10/533,377) Art Unit: 1625
Filed: November 22, 2005) Examiner: SOLOLA, Taofiq

For : HIGH PURITY PHTALEIN DERIVATIVES AND METHOD FOR
PREPARING SAME

TEST REPORT

Comparative study of the crystalline structure of fluorescein
produced according to the method of US Serial N°10/533,377 and fluorescein
produced according to the prior art

This test report aims at showing that yellow fluorescein crystals produced according to the method of claim 35 of US Serial N°10/533,377 have a different crystalline structure from the yellow fluorescein crystals produced by alkalizing and then acidifying in water.

To avoid any artifact caused by impurities present in the crystals, and to make sure to analyze only the influence of the purification process on the structure of the crystals, the tests were carried out starting from the same material, i.e. the fluorescein crystals obtained according to the method of claim 35 of US Serial N°10/533,377 (batch ADXI-26). To obtain crystals according to the prior art, crystals of the batch ADXI-26 have been dissolved in an aqueous alkaline solution and then the fluorescein molecules have been precipitated by addition of an aqueous acid solution: yellow fluorescein crystals have been harvested (batch JT-AK-TL111).

Each batch have been analysed comparatively by differential calorimetry, thermogravimetry and X-ray diffraction.

1. ANALYSED PRODUCTS

1.1 Yellow fluorescein crystals according to US Serial N°10/533,377 (batch ADXI-26)

The crystals of batch ADXI-26 have been produced according to the method of claim 35 of US Serial N°10/533,377.

1.2 Yellow fluorescein crystals according to prior art (batch JT-AK-TL111)

5g of yellow fluorescein crystals of batch ADXI-26 are solubilised in 32 mL of an aqueous solution of sodium hydroxide 1M. The dissolution of the crystals is rapid and total.

Then, 32 mL of an aqueous solution of chlorhydric acid 1M are added slowly under agitation. The fluorescein precipitates to form yellow crystals. 100 mL of purified water are added to the mix. The suspension is maintained under agitation during 30 minutes and then filtrated through a porosity filter 3. The precipitate is washed with 300 mL of purified water and then dried under vacuum at room temperature.

Mass obtained: 4.48 g

Yield: 89.6%

Product aspect: yellow powder

2. STUDY OF THE CRYSTALLINE STRUCTURE

2.1 General principle

The crystalline structure of the yellow fluorescein crystals is analysed comparatively by differential scanning calorimetry (DSC), thermogravimetry (TG) and X-ray powder diffraction (XRPD). DSC and TG are performed by an apparatus coupling these two measures.

2.2 Operating conditions

2.2.1 TG-DSC

- Equipment : Netzsch STA 449C
- Crucible Al, Atmosphere : He
- Initial temperature: 30°C, Final temperature: 360°C
- Heating speed: 5°C/min

2.2.2 XRPD

- Equipment : diffractometer Siemens D5005, scintillation detector
- anticathode Cu, Voltage: 40kV, Intensity: 40mA, θ - θ
- Room temperature
- Range of the measures: 3-30°C
- Incrementation between each measure: 0.04°C
- Time of measure by step: 4s
- Fixed slit: 1.6 mm
- Filter K β (Ni)
- Data collected and analysed with EVA software (v 12.0)

2.3 Results

2.3.1. TG-DSC

2.3.1.1 ADXI-26 - Annex 1

The thermic behaviour of ADXI-26 crystals showed:

- a continuous loss of mass (about 8.3%) from room temperature to 190°C,
- a new mass loss (about 4.9%) between 200 and 230°C,
- a little phenomenon at 280°C, without associated mass loss
- fusion-decomposition at 344°C

Complete results are shown in Annex 1. The different mass losses cannot correspond to polymorphisms but are certainly due to the release of one or more solvents. The little endothermic phenomenon observed around 280°C could be attributed to a polymorphism.

2.3.1.2 JT-AK-TL111 - Annex 2

No mass loss is observed during the heating (see annex 2). Fusion is observed at 344°C, as for ADXI-26, and preceded by an exothermic phenomenon around 250°C, probably induced by a monotropic polymorphic transformation (different from ADXI-26 crystals).

2.3.2. XRPD

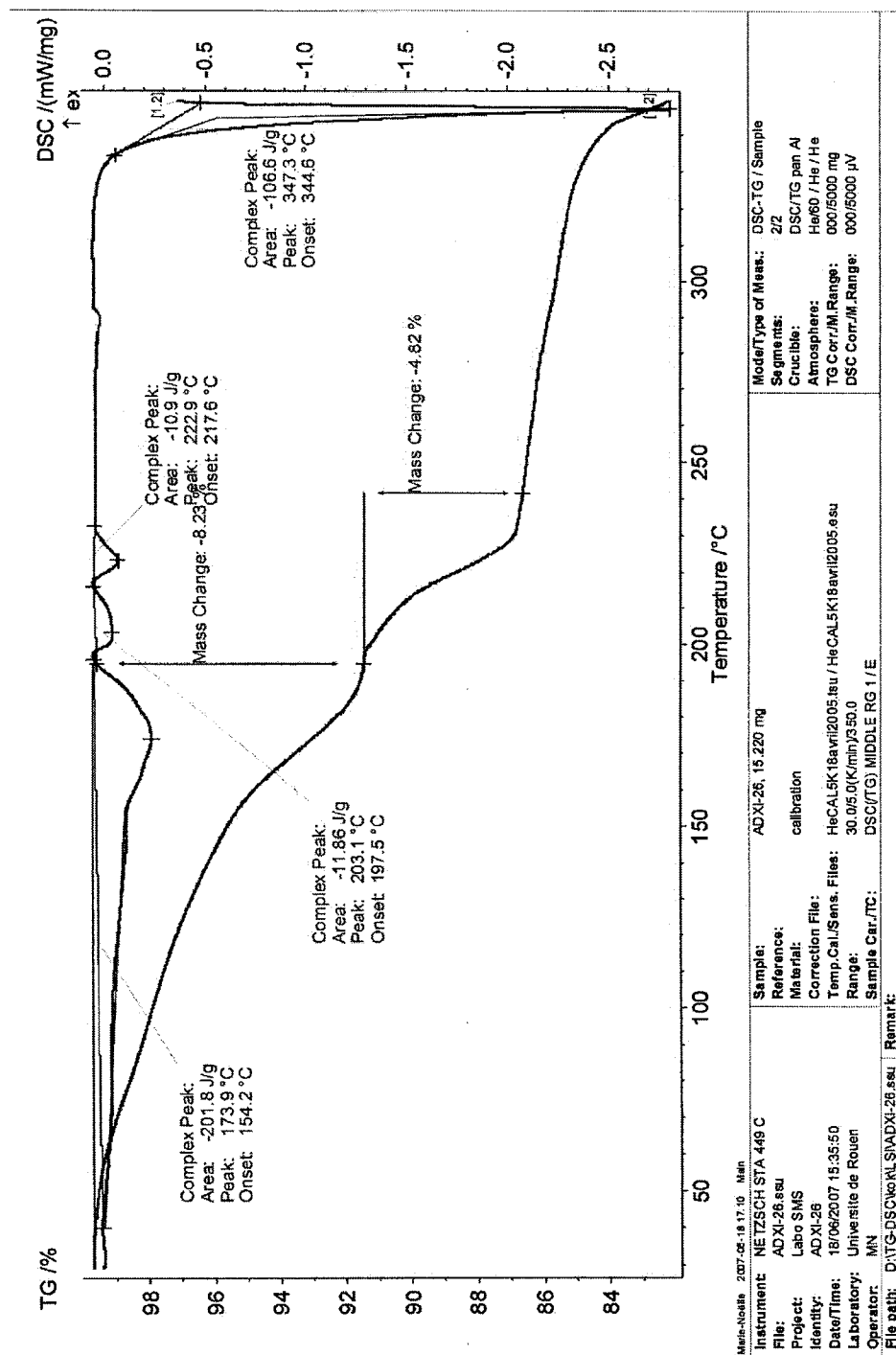
The diffraction diagram of ADXI-26 crystals is presented in annex 4, and the diffraction diagram of JT-AK-TL111 crystals is presented in annex 3. These two diffraction diagrams cannot be superimposed (see annex 5).

2.4 Conclusions

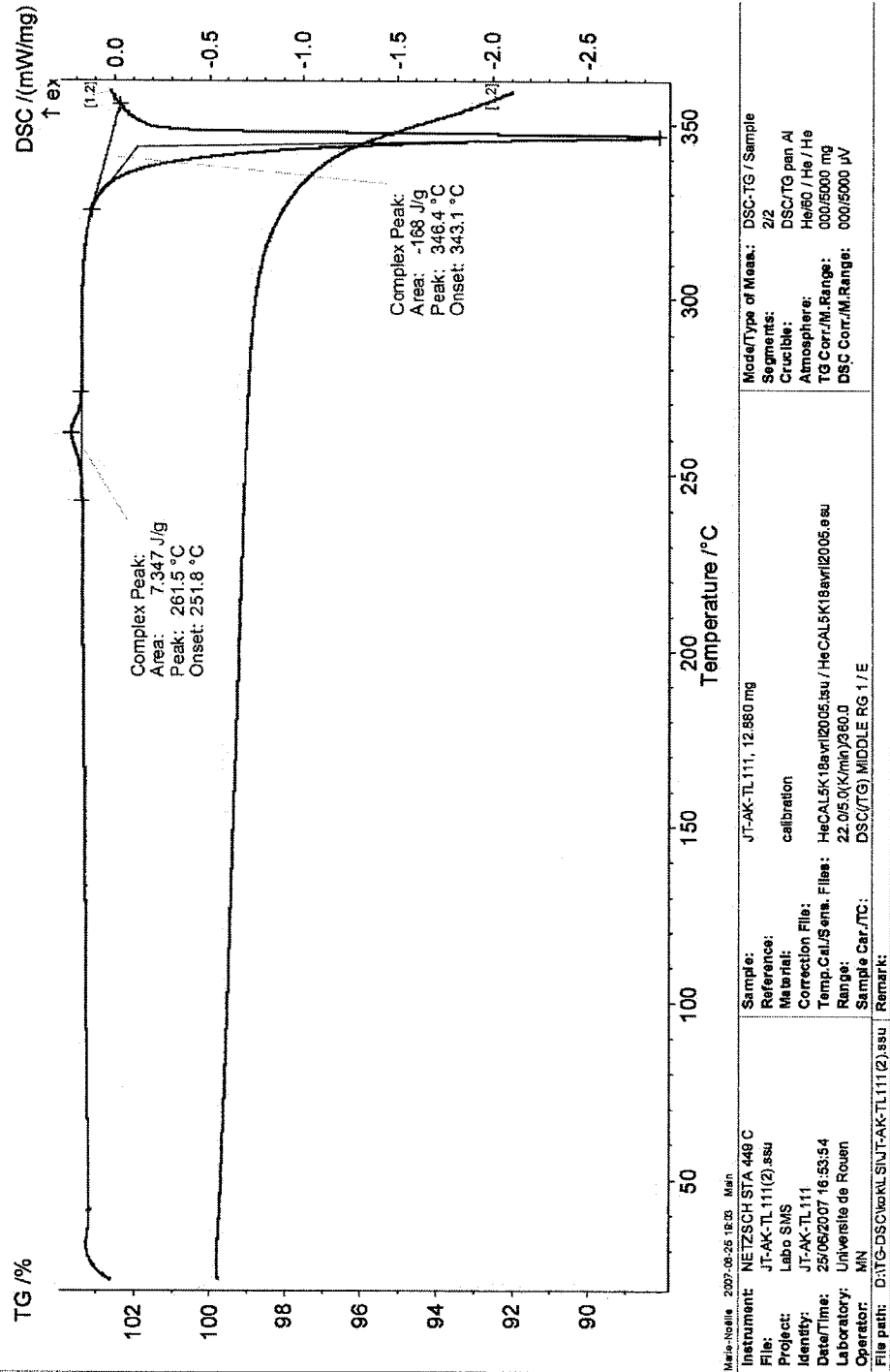
ADX1-26 and JT-AK-TL111 crystals have two different crystalline structures.

ADX1-26 crystals, i.e. the crystals produced by the method of claim 35 of US Serial N°10/533,377 have a complex structure, showing two mass losses at high temperatures.

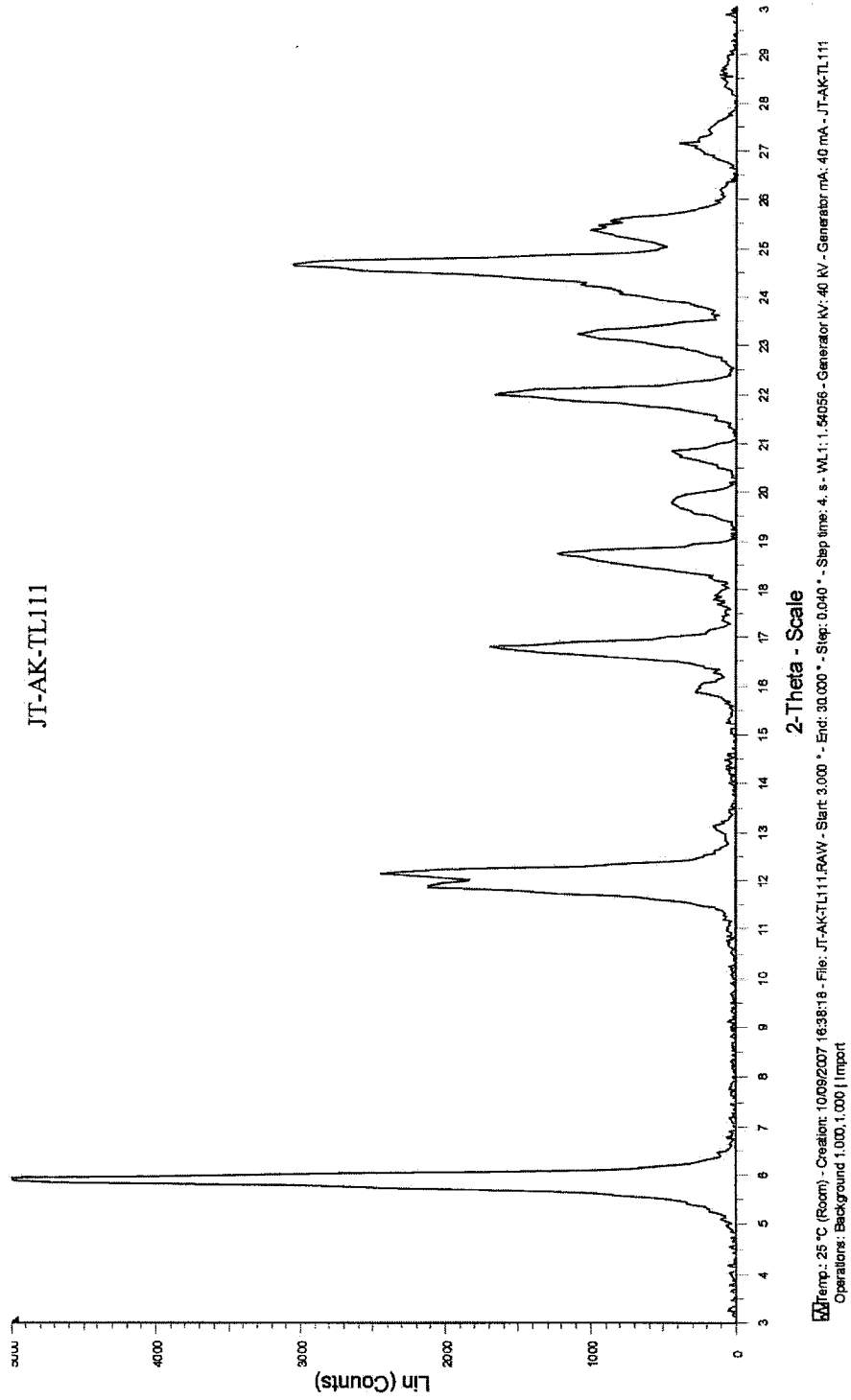
JT-AK-TL111 crystals, i.e. the crystals produced according the prior art, have a more simple crystalline structure, without any mass loss before fusion.



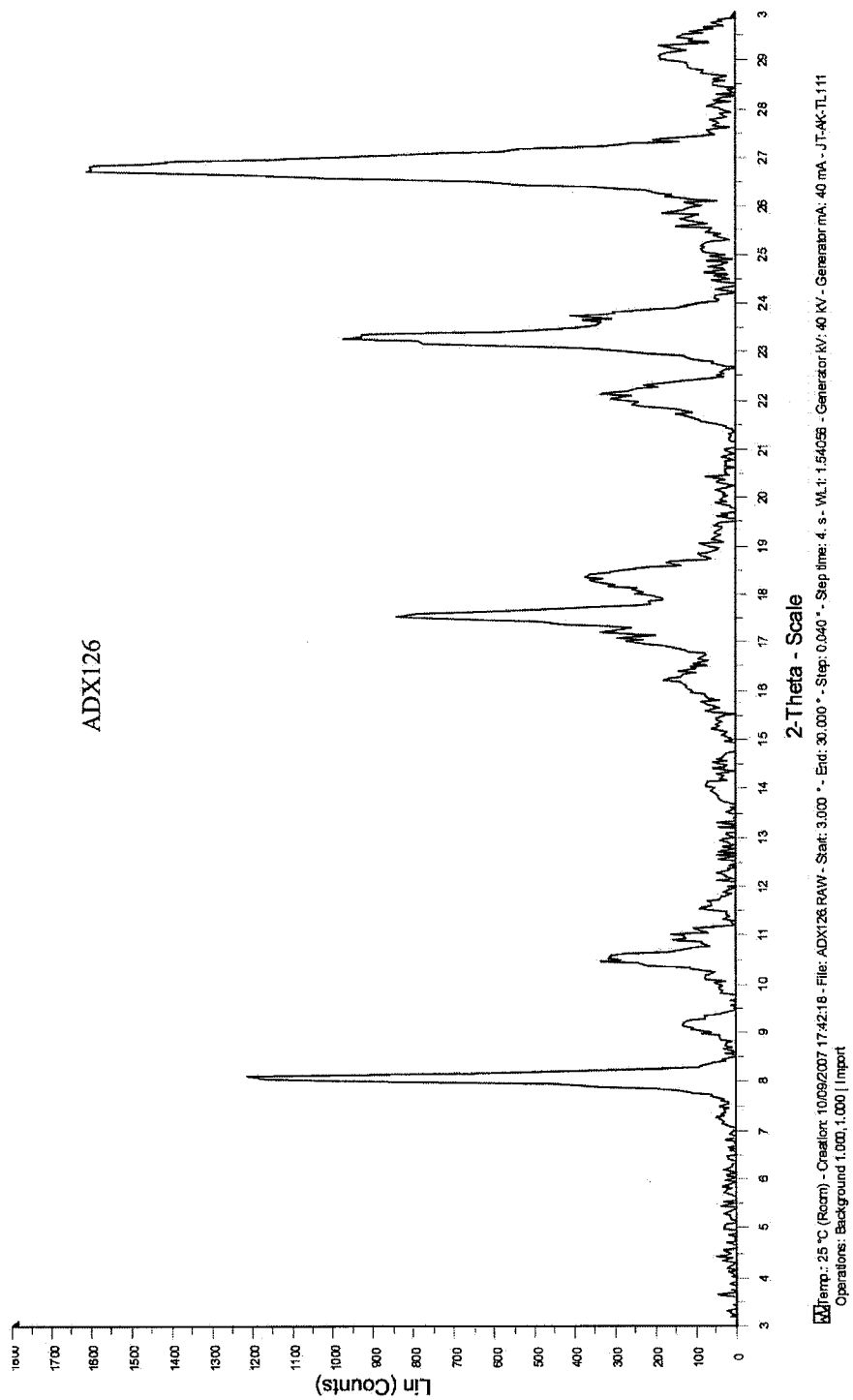
ANNEX 1



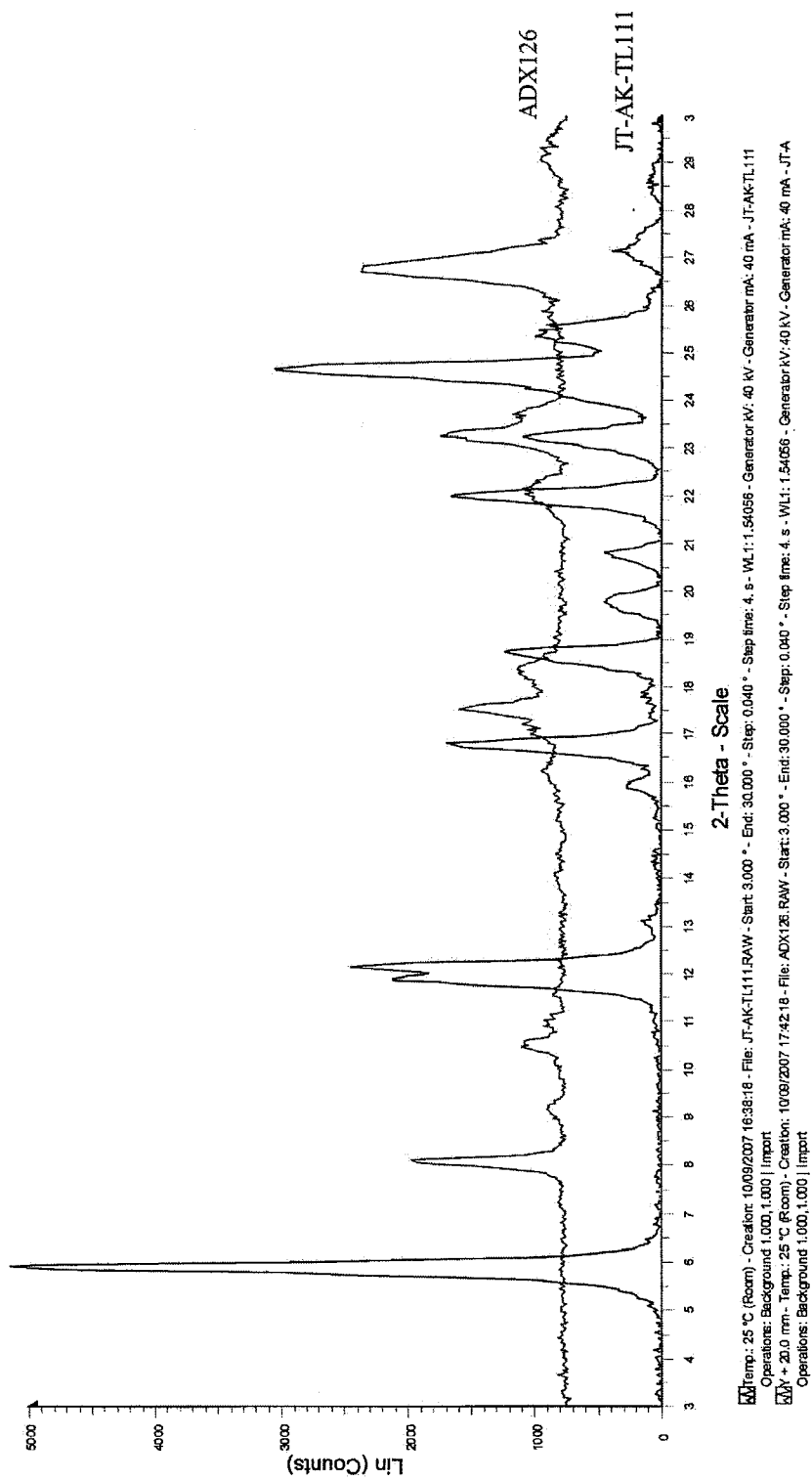
ANNEX 2



ANNEX 3



ANNEX 4



ANNEX 5

Exhibit C